

Infection (Fungal)

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Observational evaluation of sertaconazole nitrate 2.0% cream in the treatment of pruritus related to tinea pedis: A pilot study

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Introduction: Mycotic infections are extremely common, with estimates of their prevalence in the United States suggesting a lifetime risk of 10-20%. Tinea pedis (“athlete’s foot”) is the most common of all superficial cutaneous fungal infections, with topical therapy being the standard treatment. Sertaconazole Nitrate 2.0% cream (Sertaconazole), which was approved for the treatment of tinea pedis in the US in 2003, is a novel topical antifungal with broad-spectrum effects against dermatophytes, yeasts, and bacteria. Sertaconazole also has demonstrated antipruritic and anti-inflammatory properties, rendering it effective in reducing pruritus related to tinea pedis, which has been identified in controlled trials in 588 subjects; the subjects experienced rapid symptom relief in 1 week with sertaconazole. Successful elimination of persistent and annoying symptoms like pruritus may prove important in promoting patient adherence to treatment, and may also improve patients’ perceptions of their own quality of life.

Objectives: The objectives of this study were to provide evidence of the efficacy of sertaconazole nitrate 2.0% cream in reducing pruritus related to tinea pedis, in addition to accumulating quality of life data relative to its use. The rating scales used to assess these objectives included the Pruritus Visual Analog Scale (VAS) and Dermatology Quality of Life Index (DQLI).

Methods: This was a 7-day, single-center, open-label, observational pilot study in 30 male and female patients 12 years of age and older, who had been diagnosed clinically with tinea pedis. Diagnosis was confirmed by positive KOH preparation. All subjects scored >5 on the Pruritus Visual Analog Scale (VAS). Subjects received sertaconazole nitrate 2.0% cream to apply twice daily for 7 days, and were seen at baseline and on days 3 and 7. Subjects completed the Pruritus VAS and the DQLI at all 3 visits. Safety concerns were assessed at both follow-up visits.

Conclusions: Data from this study provides evidence of the usefulness of sertaconazole in reducing pruritus related to tinea pedis and thereby improving patients’ quality of life.

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Efficacy of topical onychomycosis treatments according to clinical factors

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Purpose of this study was to evaluate whether the efficacy of topical onychomycosis treatments is related to the extent of nail involvement at baseline.

Methods: An explorative analysis of drug efficacy was made in patients affected by distal subungual onychomycosis of the big toenail, positive for dermatophytes (KOH and culture), stratified according to the extent of target big toenail involvement: group A (mild, <25%), group B (moderate, $\geq 25\%$ $\leq 65\%$), group C (severe, $>65\%$). Overall, 467 patients were randomized in an unbalanced ratio 2:1:2 to a 48-week treatment with a new 8% ciclopirox nail lacquer (P-3051), based on hydroxypropyl chitosan as film forming agent, compared to its placebo vehicle and to the 8% ciclopirox market reference, based on monoester resin. "Cure" was defined as negative mycology and 100% healthy nail, "clinical success" as negative mycology and $<100\% \geq 90\%$ healthy nail, "responder" as negative mycology and $\geq 90\%$ healthy nail.

Results were available in 453 patients (P-3051 n=175, placebo n=93, reference n=185). Patients of the three groups were homogeneously distributed among treatments. In the overall sample, complete cure was 5.7% in A (n=35), 3.7% in B (n=321) and 2.1% in C (n=97); clinical success 40.0% in A, 14.6% in B and 3.1% in C; responder rate 45.7% in A, 18.4% in B and 5.2% in C. Cure was 10.0%, 6.3% and 2.6% with P-3051 in A, B and C; 5.9%, 3.1% and 2.6% with reference and 0.0% with placebo in the three groups. Responders were 50.0%, 27.0% and 7.7% with P-3051; 52.9%, 16.2% and 5.3% with reference and 25.0%, 6.2% and 0.0% with placebo. Only group B data with P-3051 were significantly different from placebo.

Conclusion: The relationship between efficacy and nail involvement was not unexpected. Our data confirm that homogeneity of stratified groups is a key factor for unbiased analyses in controlled studies. In accordance with the literature, our data confirmed a low efficacy of reference ciclopirox nail lacquer on moderate and severe onychomycosis. The efficacy of ciclopirox was definitely improved by hydroxypropyl-chitosan, which renders P-3051 effective also on moderate onychomycosis.

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Skin penetration of ketoconazole in four marketed products

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Ketoconazole is a well established treatment for seborrheic dermatitis (SD), marketed in different vehicles, including shampoos and creams. Since SD affects hair and nonhair-bearing areas, different vehicles are often prescribed for the same patient. A new foam formulation of ketoconazole for use on the scalp, body, and face provides a single formulation for multiple areas.

This study characterizes the in vitro skin permeation of ketoconazole from this novel foam in comparison to a shampoo and two creams. The in vitro skin penetration assay is a valuable tool for the study of percutaneous absorption. The assay uses freshly excised human abdominal skin from elective surgeries. The subcutaneous fat is removed, and the skin is dermatomed to a thickness of 0.25mm. The specimen, consisting of stratum corneum, epidermis and partial dermis, is mounted in flow-through diffusion cells, which are temperature controlled to match real use (in-vivo) conditions. Skin penetration of ketoconazole from the foam applied to the stratum corneum surface was compared to penetration from a marketed shampoo and two creams. Receptor fluid was collected every hour for up to 6 hours. At six hours post-application, skin was washed, tape-stripped twice, and then the epidermis was separated from the dermis using a heat block. Each formulation was tested on 3 separate donors (4 replicates each; n≥18). Drug content was measured by LC/MS/MS with an LLOQ of 50 pg/mL.

The foam delivered 4 fold and 45 fold more ketoconazole through the skin over 6 hours compared to the creams and shampoo respectively. Significant increases in ketoconazole delivery from the foam could be seen as early as 1 hour. The epidermal skin distribution showed a 3 fold increase in ketoconazole delivery from the foam compared to the creams. The results from this study suggest that in addition to its versatility, the foam enhances penetration of ketoconazole when compared to shampoos and creams.

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Pharmacokinetics of posaconazole in skin following oral administration

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While azoles such as itraconazole are used to treat dermatophytic skin and nail infections, complete cure rates remain low, and patients often experience significant recurrence. Terbinafine, an allylamine, demonstrates greater efficacy compared with itraconazole, but approximately 60% of patients fail to achieve complete cure. Posaconazole (POS) has established clinical efficacy in patients with, and at high risk for, invasive fungal infection. While in vivo data demonstrating the efficacy of POS against dermatophytic skin and nail infections are not available, in vitro activity of POS suggests a potential therapeutic benefit for these infections. We assessed POS concentration in 4-mm skin punch biopsies in 30 healthy adult subjects administered POS 400 mg twice daily (BID) orally for 8 days with a high-fat meal. Blood and skin samples were collected at prespecified times on Day 1 and Day 8. From each subject, two skin samples were obtained: one immediately before or after both the first and last doses of POS. A MIC₉₀ value of 250 ng/ml, which encompasses the majority of common dermatophytes,¹ was used to calculate the PK/PD parameters AUC (0-24hr)/MIC₉₀ and time-above-MIC₉₀ in plasma and skin. On Days 1 and 8, POS attained peak plasma concentrations at a median T_{max} of 8 and 5 hours, and peak skin concentrations at 12 and 3 hours, respectively. On Day 1, the AUC/MIC₉₀ ratio was 29 and 14 in plasma and skin, respectively. These ratios increased to 149 and 187 in plasma and skin, respectively, on Day 8. POS concentrations in skin and plasma were severalfold higher than the MIC₉₀ for the entire dosing interval on Day 8. AUC/MIC₉₀ ratio in skin and plasma was similar. POS dosed at 400 mg BID orally was safe and well tolerated among healthy subjects. In conclusion, POS given orally to healthy subjects at 400 mg BID for 8 days resulted in skin concentrations that were severalfold above the MIC₉₀ value for dermatophytes¹ commonly seen in cutaneous infections. These data suggest that posaconazole may be a favorable option for treatment of dermatophytic skin and nail infections.

1. Gupta AK, Kohl Y, Batra R. In vitro activities of posaconazole, ravuconazole, terbinafine, itraconazole and fluconazole against dermatophyte, yeast and non-dermatophyte species. *Med Mycol.* March 2005;43;179-185.

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